INTESTINAL ABSORPTION OF RADIOIODIDE IN RATS EXPOSED TO HYPOXIA (380 mm Hg) AND FOOD DEPRIVATION

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RESEARCH REPORT

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FOREWORD

The present investigation was supported by Public Health Service Research Grant No. GM-05112 from the National Institute of General Medical Sciences, National Institutes of Health, Bethesda, Maryland. This report was prepared by Peter F. Pearson and was submitted to the Graduate School in partial fulfillment of the requirements for the degree of Master of Science at The Pennsylvania State University. The research was conducted by Mr. Pearson as a subproject of a research project entitled "Biophysical and Endocrine Changes in Acclimated Rats" with Dr. Adam Anthony, Professor of Zoology, acting as the project director and Dr. G. K. Strother, Associate Professor of Biophysics, as co-investigator. This work was also aided in part by funds from NASA Grant NGR-39-009-115.

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The experiments reported herein were conducted according to the principles outlined in the "Guide for Laboratory Animal Facilities and Care" and adopted by the Institute of Laboratory Animal Resources, National Academy of Sciences-National Research Council.

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INTRODUCTION

For several decades since LeBlond (18) reported that thyroidectomized rats are more resistant to altitude hypoxia, there has been continued interest in determining the specific role of the thyroid during hypoxia acclimation. There is almost universal agreement that prolonged hypoxia exposure results in decreased thyroidal function; on the other hand, the thyroidal response during "acute" hypoxia has not been fully clarified.

Largely on the basis of thyroidal I-131 uptake and turnover measurements, both a depression (34, 35) and an increase (9, 8) in thyroid activity have been reported during acute hypoxia exposure. Recently, Nelson (21) and Surks (27) suggested that hypoxia-induced alterations in dietary intake of iodine might account for some of the conflicting reports in the literature. This suggestion merits consideration since aphagia is known to regularly accompany exposure to hypoxia. Thus, a hypothyroid rat would exhibit an increased thyroidal uptake of injected I-131 as a result of an iodine insufficient state brought about by reduced dietary intake of iodine. On the other hand, the hypothyroid rat would exhibit a reduced I-131 uptake in the presence of normal circulating levels of iodine.

In any event, it is evident that a study of the effects of hypoxia on the rate of gastrointestinal iodide absorption, in relation to circulation levels, should add to our overall understanding of the role of the thyroid during the onset of acclimation.

Thus, the aim of the present study is to establish the effects of hypoxia on gastrointestinal absorption of orally administered radioiodide and to determine the extent to which this influences circulating and thyroidal iodide levels.

GENERAL CONSIDERATIONS

Before describing the methods used it is desirable to review certain basic aspects of thyroid function and the present state of knowledge regarding the effects of hypoxia exposure on gastrointestinal function.

A. Thyroid Regulation and Physiology.

Pitt-Rivers and Tata (23) divide thyroid activity into three stages: (1) iodide uptake, (2) synthesis and storage of thyroxine, and (3) release of thyroxine. Iodide uptake by the thyroid is considered to be relatively independent of pituitary thyrotropin (TSH) regulation, whereas the synthesis and secretion of thyroid hormone is under TSH control.

Dietary iodine is the major source of thyroidal iodide. No appreciable iodide absorption occurs in the stomach (2), so the main site of absorption is the small intestine (26, 1, 22, 16). Thus, any delay in the passage of food in the duodenum would effectively reduce the net rate of absorption of iodide into the circulation.

The thyroid can extract small amounts of iodide from blood by a very efficient active transport mechanism so that the normal thyroid iodide:serum iodide ratio (T/S) is generally 20:1. Iodide that is incorporated into the gland is immediately oxidized to elemental iodine by a peroxidase reaction (10, 36).

Synthesis of thyroxine is by iodination of tyrosine present as a tyrosyl radical of thyroglobulin. Steps involved consist of first iodinating tyrosine to form monoiodotyrosine (MIT), adding another iodine to form 3,5-diiodotyrosine (DIT) and then coupling two DIT molecules through a phenolic bridge with a loss of alanine to form thyroxine (T_4). Another compound triiodothyronine (T_3) can be formed by coupling MIT and DIT molecules or by partial deiodination of T_4. These steps occur in the epithelial cells and the resulting hormone is stored in the form of thyroglobulin in the lumen of the thyroid follicle.

Proteinases continually degrade the thyroglobulin into its component parts: MIT, DIT, T_3 and T_4. Normally MIT and DIT are rapidly dehalogenated with the iodide reclaimed by the gland. T_3 and T_4 are released into the circulation bound to two serum proteins, thyroxine binding globulin (TBG) and thyroid binding prealbumin (TBPA) which are involved in the transport and peripheral metabolism of thyroid hormones.

Excretion of metabolites of thyroid hormone degradation can occur via the renal or gastrointestinal routes. Chromatographic analysis reveals that iodide is excreted in the urine as inorganic iodide (23, 28) and in the feces as organically bound iodide (17).

TSH (thyroid stimulating hormone) produced in the anterior pituitary forms the necessary link in the regulation of iodine metabolism. It stimulates the thyroid to produce and release T_4. TSH secretion is regulated in part by a direct inhibitory feedback

of high circulating T_4 levels and by neural mechanisms operating through the hypothalamus. Stimulation of the lateral area of the hypothalamus causes the release of TRF (thyrotropin releasing factor) which in turn stimulates TSH release by the anterior pituitary (19).

B. Effects of Hypoxia Exposure on Thyroid and Gastrointestinal Function.

Low thyroid function has long been suspected to be beneficial to organisms exposed to reduced pressures (7), presumably because hypothyroidism lowers oxygen consumption of the intact animal and therefore reduces its oxygen requirements. It is known that thyroidectomy increases survival time of rats during hypoxia exposure (17, 13, 37). Other workers (35, 34, 21, 27) have shown that a decreased thyroid function occurs following prolonged hypoxia exposure. However, the precise thyroidal changes that occur at the onset of hypoxia exposure haven't been completely explained as evidenced by conflicting reports relating to the effects of acute hypoxia on thyroidal iodide uptake.

Several workers have noted that hypoxia exposure can inhibit motility of the gastrointestinal tract with the extent of inhibition proportional to the severity of exposure. A delay in gastric emptying time has been observed in the laboratory rat (6, 5). Van Liere et al. (30) using dogs and LeBlond (18) using rats also report the presence of undigested food in the stomachs after 24 hours exposure at 20,000 feet. The mechanism postulated for this is a vagospastic pylorospasm resulting in pyloric sphincter closure due to low oxygen tension stimulation of the vagus nerve (6). In addition, the tone and motility of rat intestines both in vivo and in vitro are reported

to be decreased by high altitude exposure (29, 11).

The gastrointestinal tract alterations that occur have an effect on the transport of ingested substances to the small intestine. Since dietary iodide is the main source of thyroidal iodine, the iodide pool available for absorption and subsequent thyroidal uptake can presumably be altered.

Restatement of the Problem

The possibility that dietary iodide may play a functional role in thyroidal response during acute hypoxia is examined in the present study. The specific objectives of this study are to determine:

1. The effects of acute hypoxia (380 mm Hg) on absorption of food and of orally administered I-131.
2. The effects of acute hypoxia on circulating radioiodide levels.
3. The effects of acute hypoxia on the excretion pattern of radioiodide.
4. The effects of acute hypoxia on thyroidal uptake of I-131 relative to existing circulating radioiodide levels.
5. The extent to which food deprivation affects iodide absorption and subsequently the circulating, thyroidal, urinary and fecal levels of I-131.

MATERIALS AND METHODS

A total of 48 male albino rats (Holtzman, Madison, Wisconsin) weighing 200-300 gm was employed in this study. All animals were housed in groups of 6 in 22" x 15" stainless steel cages, maintained on Wayne Lab-blox (containing 1.5 μg of iodine per gram) and tapwater *ad libitum* and allowed to adapt to laboratory conditions for one to two weeks prior to experimentation

The altitude chamber used was the same as that employed by Anthony *et al.* (3). The total chamber volume is 286 cubic feet. Estimated turnover of air is about 8 cubic feet per minute when the chamber is maintained at one-half atmospheric pressure. The temperature within the chamber was 26±1 C while that of the room housing the control rats was 25±1 C.

Experimental rats were exposed to a simulated altitude of 18,000 feet (380 mm Hg) for a period of 24 hours. Control animals were maintained at ambient pressure (725 mm Hg at University Park). Two experiments were performed. The first involved measurements of iodide metabolism and excretion rates in ambient pressure control and hypoxic rats fed on an *ad libitum* regimen. These are referred to as Groups A and B, respectively. Since it was observed that hypoxia-exposed rats consume very little food during the first 24 hours of exposure, it was desirable to examine the possible effects of food deprivation on iodide absorption. Therefore, a second experiment was carried out which involved identical measurements of

iodide metabolism. One group of rats was food deprived at ambient pressures for 24 hours, given an oral dose of NaI-131 and fed ad libitum at ambient pressure for the 24 hour test period. A second group was food deprived for 24 hours at ambient pressure, given an oral dose of NaI-131 and exposed to hypoxia for 24 hours. These groups are designated as C and D, respectively.

The experimental procedure was follows: Rats in Groups A, B and C were weighed, placed in individual metabolic cages and force fed 0.2 μc (0.1-0.2 ml) of NaI-131 (Iodotope, Squibb) in 2 gm of an iodine deficient diet containing 15 μg I/Kgm food (Nutritional Biochemicals Corp.) at time zero of the experiment (25). Rats in Group D received the same oral dose of radioiodide after a preliminary 24 hour period of food deprivation and then were placed in the decompression chamber. An equal volume of iodotope was placed in a graduated centrifuge tube to serve as a counting standard. At the end of the 24 hour period the rat was reweighed and anesthetized with pentobarbital sodium (6 mg per 100 mg body weight, injected intraperitoneally).

Whole blood was then obtained by cardiac puncture. Aliquots were placed in heparinized centrifuged tubes and spun down for 20 minutes. One ml of plasma was removed and counted. The gastrointestinal tract was removed and divided into two sections, the stomach and the intestines from the pyloric sphincter to the caecum. Each section was weighed, flushed with physiological saline to remove all contents which were counted for radioactivity. Each

section was reweighed to determine the weight of its contents and then counted. The thyroid was removed, cleaned of excess tissue, weighed on a torsion spring balance and then counted. Urine and fecal samples were also collected and counted.

Each sample was monitored for radioactivity in a well-type scintillation counter with a 1 7/8" NaI thallium activated crystal (Nuclear Chicago Corp., model 181-A). All samples were counted three times at an operating voltage of 1400 volts. All counts were corrected for background and isotopic decay.

Statistical analyses of data were performed using the following formulas:

1. Standard deviation (σ) and standard error (SE) where d refers to the sum of the deviations from the mean and n the number of sample values;

$$\sigma = \sqrt{\frac{\sum d^2}{n-1}} \qquad SE = \frac{\sigma}{\sqrt{n}}$$

2. Probability levels were calculated using the t test where:

$$t = \frac{Ma - Mb}{\sqrt{(SE_a)^2 + (SE_b)^2}}$$

The subscripts a and b refer to the two groups compared and M is the mean of each group. These tests are outlined in Ganong (12).

RESULTS

The major findings are presented under the following headings: A. Effects of hypoxia and food deprivation on gastrointestinal absorption of orally administered NaI-131; B. Effects of hypoxia and food deprivation on gastrointestinal food content; C. Plasma and thyroidal radioiodide levels in hypoxia-exposed and food-deprived rats; D. Radioiodide excretion in hypoxia-exposed and food-deprived rats; E. Body weight changes in hypoxia-exposed and food-deprived rats.

In all groups the percent recovery of orally administered I-131 varied from 50-67 percent. That part not recovered was presumably taken up by tissues not analyzed in this study. The results are summarized graphically in Figures 1-8 with tabular data included in the Appendix.

For ease of comparison data from two separate experiments are combined in all figures. Thus, Groups A and B (experiment one) refer to control and hypoxia-exposed rats fed ad libitum, whereas Groups C and D (experiment two) represent food-deprived rats kept at ambient pressure or at reduced pressure.

A. Effects of hypoxia and food deprivation on gastrointestinal absorption of orally administered NaI-131.

Figures 1 and 2 summarize data on 24 hour gastrointestinal absorption of NaI-131 in hypoxic and control rats fed on an ad libitum regimen; they also demonstrate effects of food deprivation

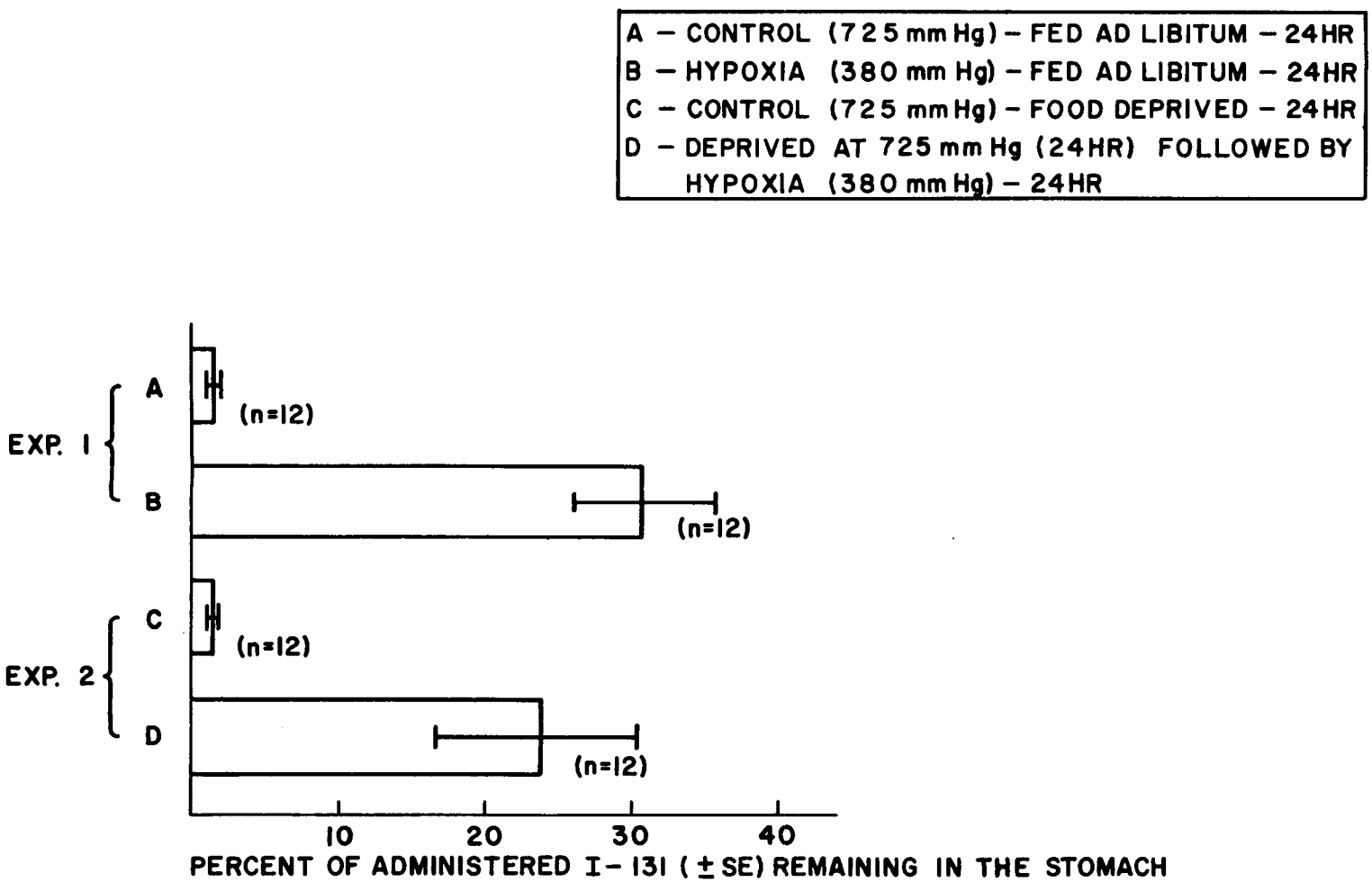

FIG. 1 EFFECTS OF HYPOXIA AND FOOD DEPRIVATION ON GASTRIC CONTENT OF I-131 IN HOLTZMAN RATS GIVEN AN ORAL DOSE OF 0.2 μc OF Na I-131 AT TIME ZERO

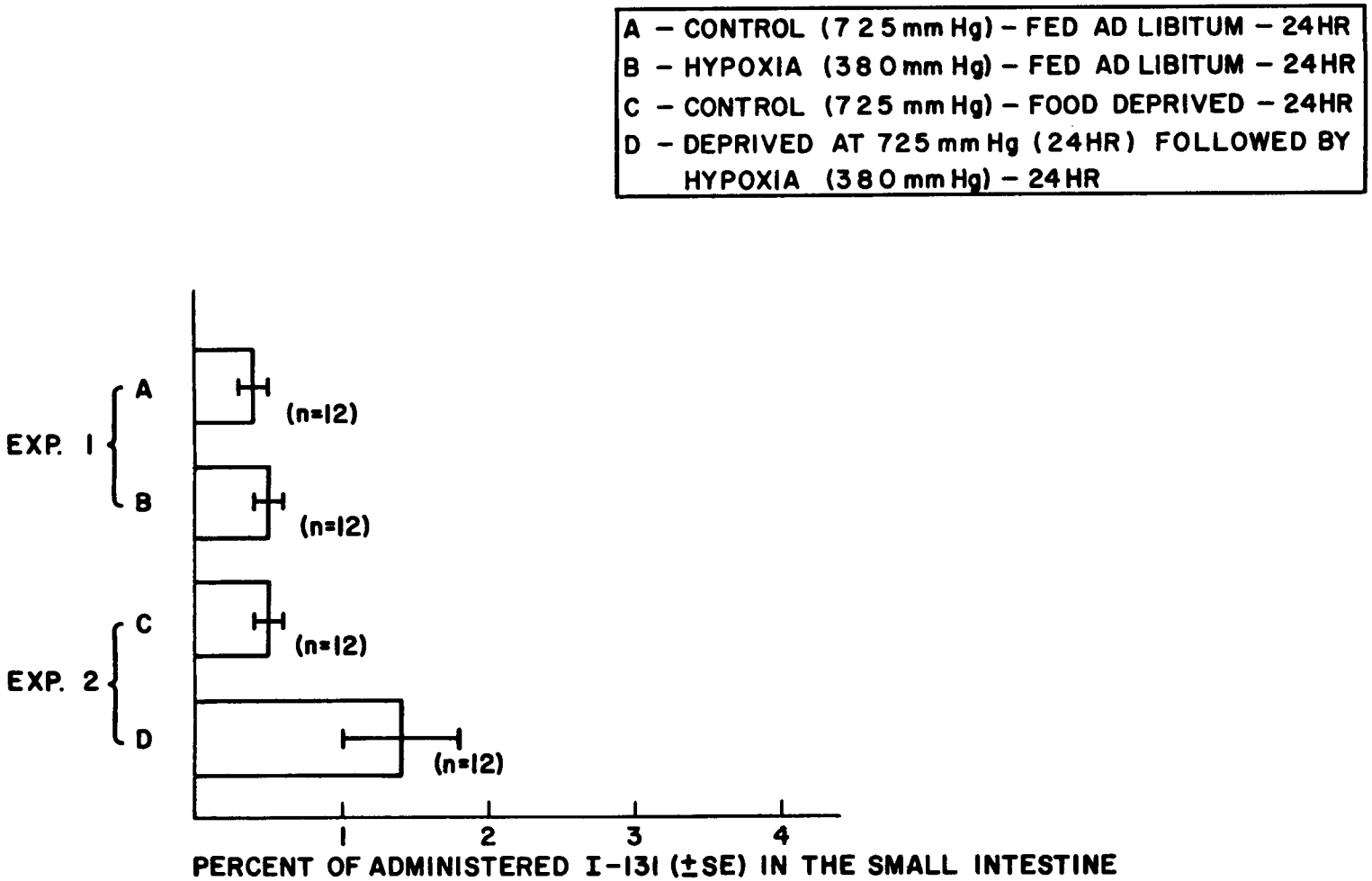

FIG. 2 EFFECT OF HYPOXIA AND FOOD DEPRIVATION ON INTESTINAL ABSORPTION OF I-131 IN HOLTZMAN RATS GIVEN AN ORAL DOSE OF 0.2μc OF NaI-131 AT TIME ZERO

at ambient pressure (Group C) and at reduced pressure (Group D) on the 24 hour NaI-131 absorption in the stomach and intestine.

The major finding from experiment one was that gastric iodide content of hypoxic rats was markedly higher than that of controls (Figure 1, Groups A and B). Since it is known that iodide absorption does not occur in the stomach, this leaves no question that hypoxia exposure causes a delay in movement of food containing iodide from the stomach to the duodenum. Intestinal levels of iodide, however, proved to be comparable in both controls and hypoxic rats (Figure 2, Groups A and B). Since less radioiodide reached the intestine in hypoxic rats than in controls, these data indicate that hypoxia also causes a reduced intestinal absorption from the intestinal tract.

Data from experiment two reveal that the stomach and intestinal radioiodide content of food-deprived rats at ambient pressure (Group C) was the same as that of rats fed ad libitum. On the other hand, when food-deprived rats were subjected to hypoxia (Group D) it was found that both stomach and intestinal radioiodide content was higher than in controls. Thus, both experiments clearly show that hypoxia exposure results in a net decrease in gastrointestinal absorption of iodide.

B. Effects of hypoxia and food deprivation on gastrointestinal food content.

Analysis of actual food content in the stomach and intestines of hypoxia-exposed and food-deprived rats supports the observation of Subsection A. Hypoxic rats maintained on the ad libitum food

regimen had 3.5±0.4 gm of food in the stomach and 2.5±0.3 gm in the intestine. The stomach and intestines of the control rats, on the other hand, had 0.3 gm and 1.3 gm, respectively.

Food-deprived, hypoxia-exposed rats also had a marked increase in gastric, but not intestinal, food content (Figure 3, Group D). It was further observed that the stomach and intestinal content of food in food-deprived rats at ambient pressure (Group C) was as great as that of the controls fed ad libitum (Group A). This indicated an apparent decrease in food absorption brought about by food restriction.

In summary, measurements of food content indicated that the major effect of hypoxia, with or without prior food deprivation, was a delay in the gastric emptying of food.

C. Plasma and thyroidal levels in hypoxia-exposed and food-deprived rats.

Figures 4 and 5 summarize data on the effects of hypoxia and food deprivation on circulating levels and thyroidal content of radioiodide, respectively. The major finding from experiment one was that the plasma radioiodide level of hypoxic rats was comparable to that of controls (Figure 4, Groups A and B). In addition, the thyroidal radioiodide content of hypoxic rats relative to ad libitum controls was reduced (Figure 5, Groups A and B). Data from experiment two reveal that food deprivation at ambient pressure has little effect on circulating plasma levels of radioiodide relative to ad libitum controls (Figure 4, Groups A and C), whereas there is an

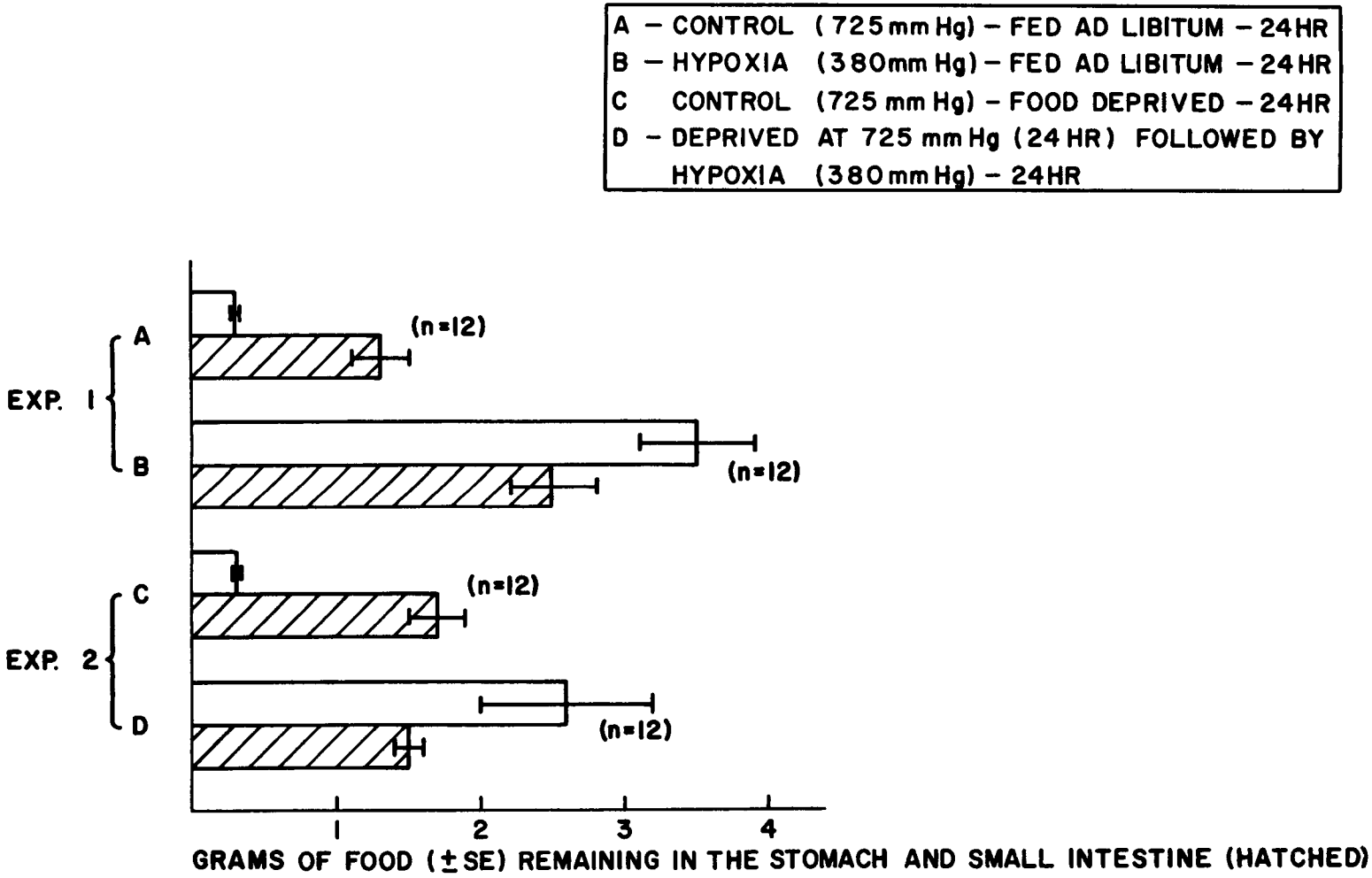

FIG. 3 EFFECTS OF HYPOXIA AND FOOD DEPRIVATION ON GASTROINTESTINAL ABSORPTION OF FOOD IN HOLTZMAN RATS GIVEN AN ORAL DOSE OF 0.2μc NaI–131 AT TIME ZERO

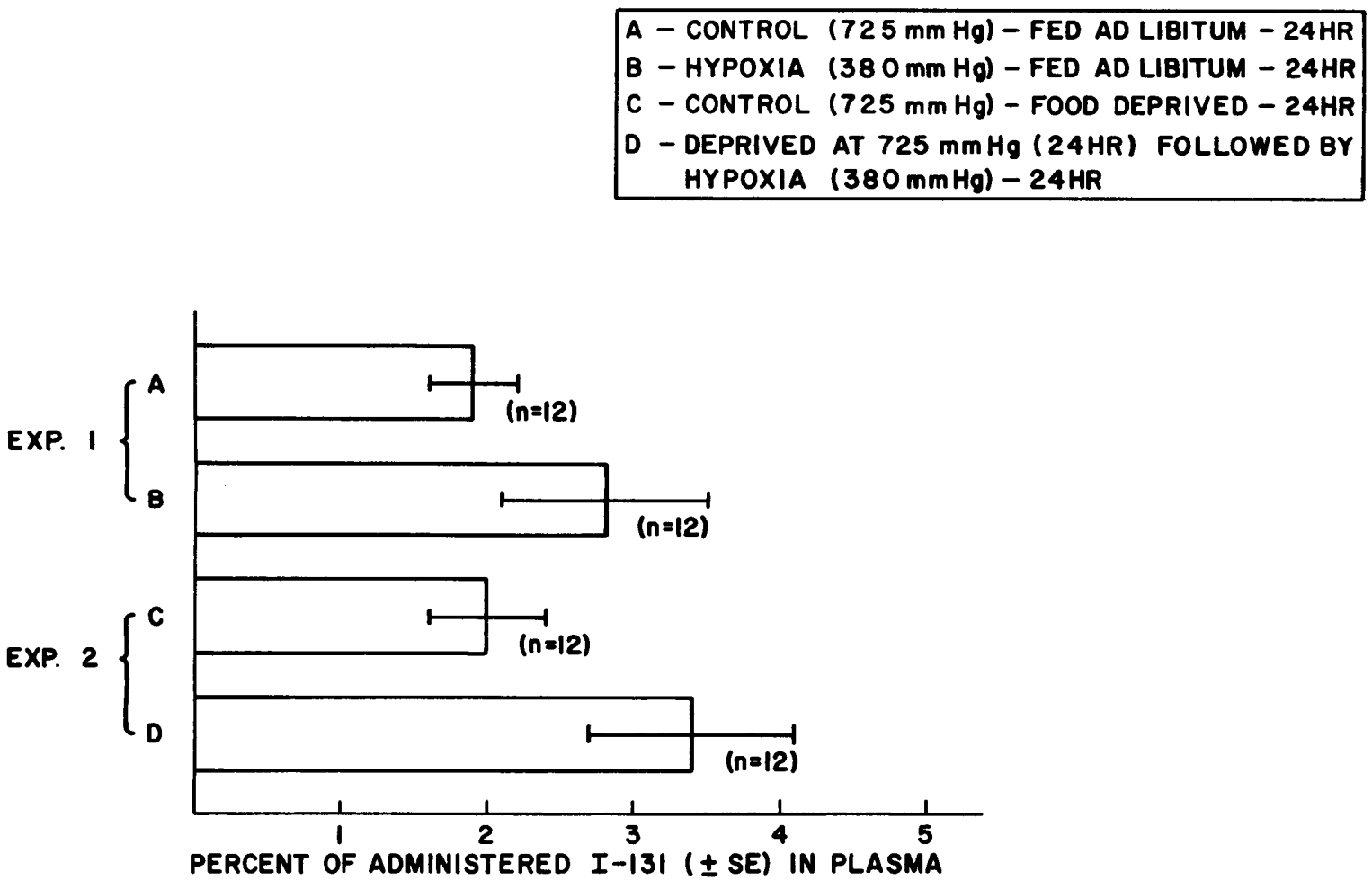

FIG. 4 PLASMA RADIOIODIDE LEVELS IN HYPOXIC AND FOOD DEPRIVED HOLTZMAN RATS GIVEN AN ORAL DOSE OF 0.2 μc Na I – 131 AT TIME ZERO

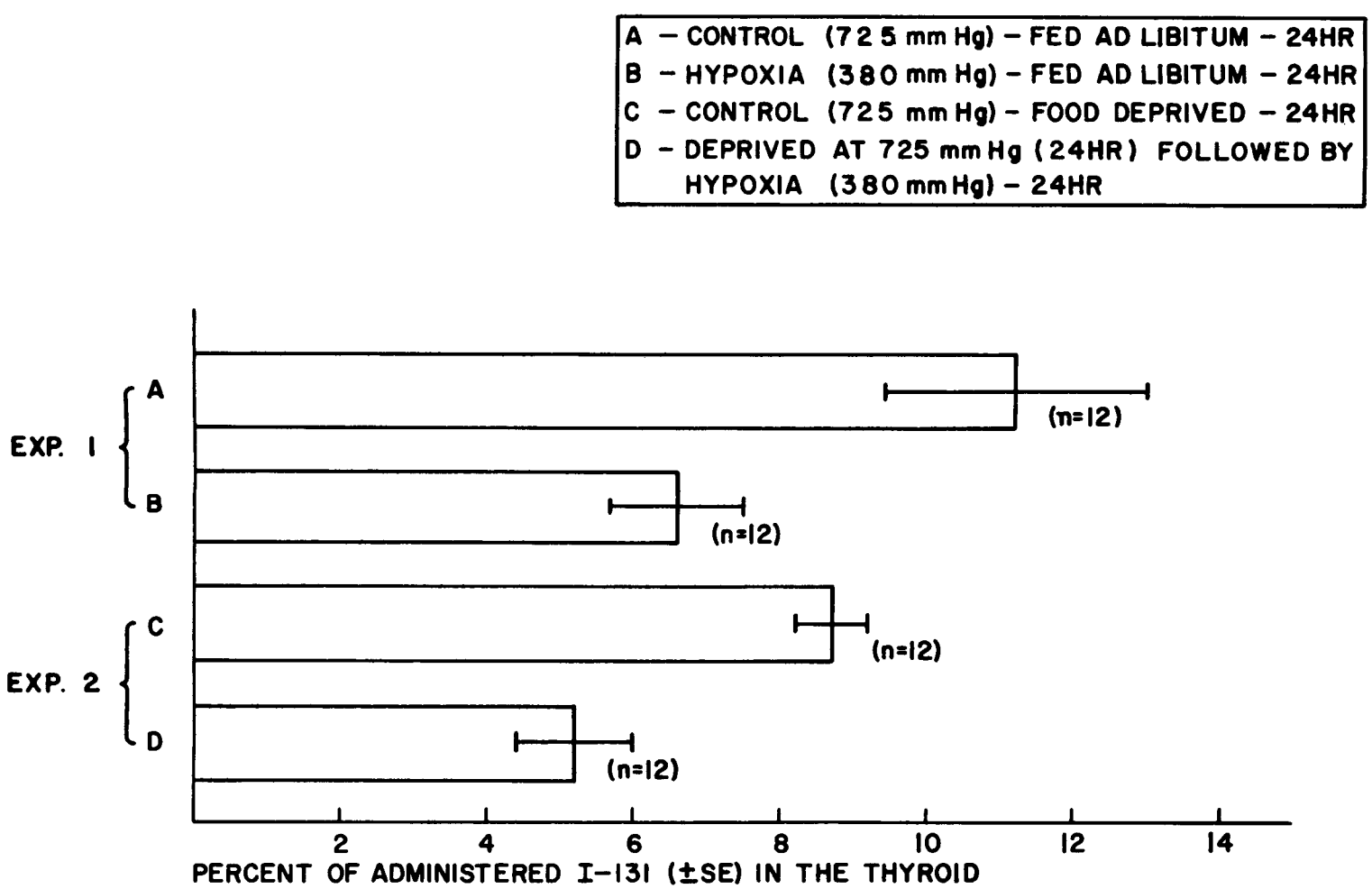

FIG. 5 EFFECTS OF HYPOXIA AND FOOD DEPRIVATION ON THE THYROIDAL CONTENT OF RADIOIODIDE IN HOLTZMAN RATS GIVEN AN ORAL DOSE OF 0.2 μc NaI-131 AT TIME ZERO

apparent decrease in thyroidal iodide content (Figure 5, Groups A and C). When rats were food deprived at ambient pressure and subsequently exposed to hypoxia, they exhibited a plasma radioiodide level which was comparable to that of food-deprived controls (Figure 4, Groups C and D). In addition, a decreased thyroidal radioiodide content was observed (Figure 5, Groups C and D). Thus, both experiments indicate there is a reduced thyroidal uptake in hypoxia-exposed rats.

D. Radioiodide excretion in hypoxia-exposed and food-deprived rats.

Analyses of urinary and fecal radioiodide excretion support the above findings. Figures 6 and 7 summarize the effects of hypoxia and food deprivation on urinary and fecal radioiodide levels, respectively. It can be seen that there was a marked reduction in urinary radioiodide excretion of hypoxia-exposed rats relative to controls (Figure 6, Groups A and B). Data from the second experiment reveal that food deprivation alone has little effect on urinary radioiodide excretion (Figure 6, Groups A and C). However, when rats were food-deprived and then subjected to hypoxia exposure, there was a marked reduction in urinary excretion of radioiodide (Groups C and D). The 24 hour urine volume of hypoxic rats was not found to be significantly lower than that of controls (Table 6, Appendix).

There was no difference in the fecal radioiodide excretion of control and hypoxia-exposed rats (Figure 7, Groups A and B). Food-deprived, hypoxia-exposed rats (Group D), on the other hand, exhibited a marked decrease in fecal radioiodide content.

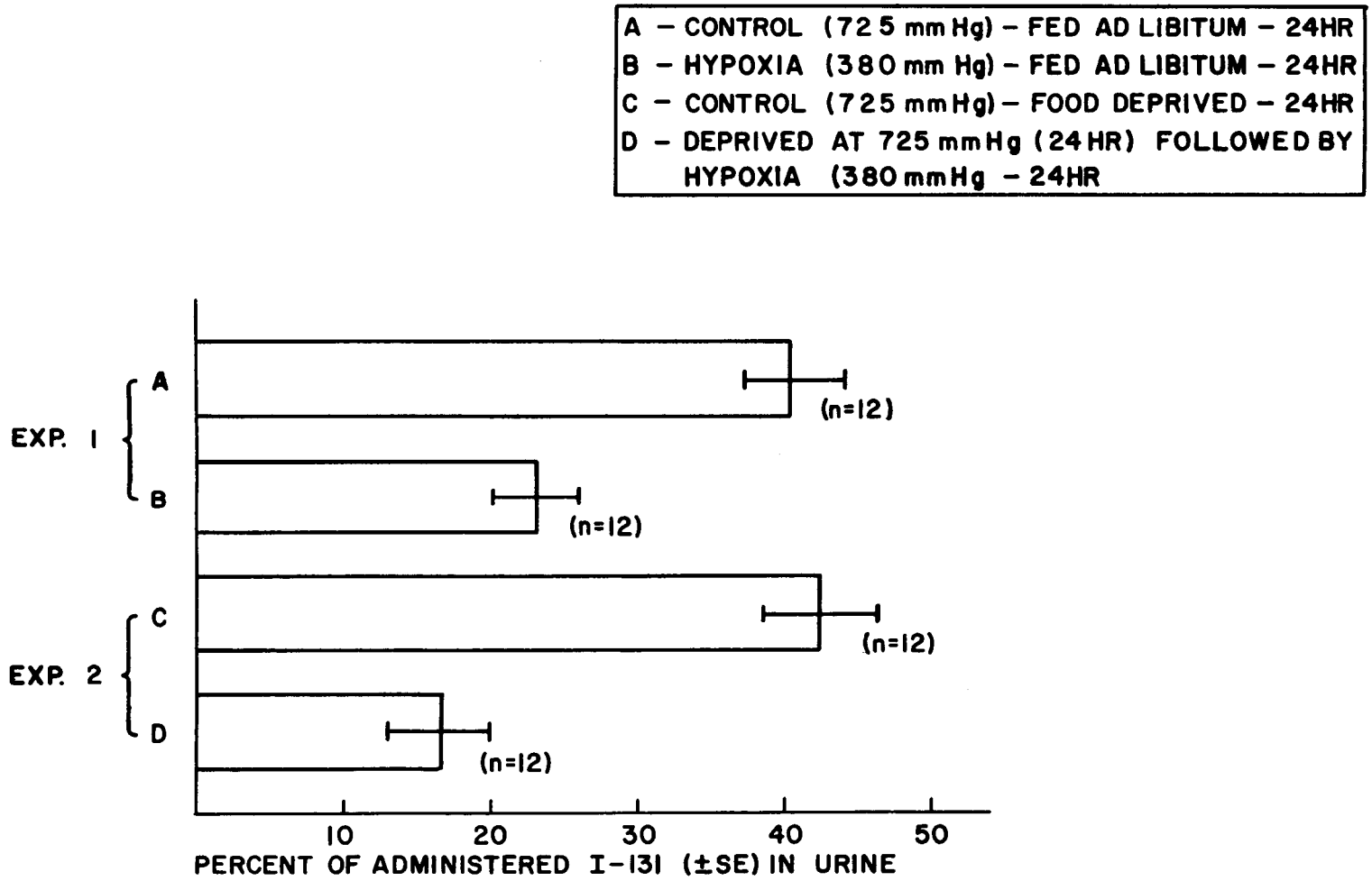

FIG. 6 EFFECTS OF HYPOXIA AND FOOD DEPRIVATION ON URINARY RADIOIODIDE LEVELS IN HOLTZMAN RATS GIVEN AN ORAL DOSE OF 0.2μc Na I-131 AT TIME ZERO

A – CONTROL (725 mm Hg) – FED AD LIBITUM – 24HR
B – HYPOXIA (380 mm Hg) – FED AD LIBITUM – 24HR
C – CONTROL (725 mm Hg) – FOOD DEPRIVED – 24HR
D DEPRIVED AT 725 mm Hg (24HR) FOLLOWED BY HYPOXIA (380 mm Hg) – 24HR

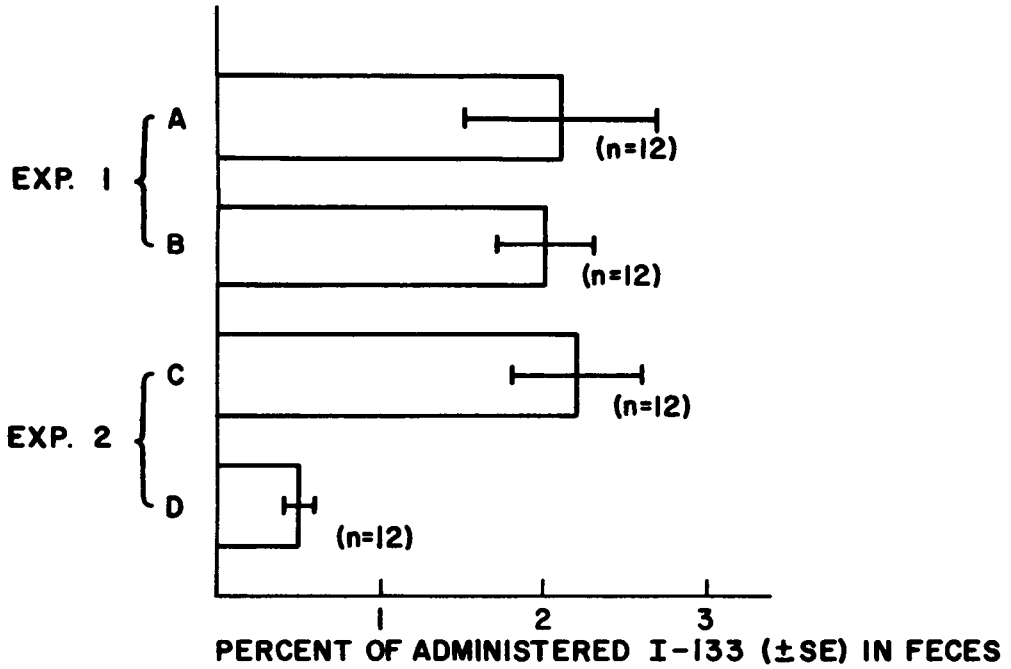

FIG. 7 EFFECTS OF HYPOXIA AND FOOD DEPRIVATION ON FECAL RADIOIODIDE EXCRETION OF HOLTZMAN RATS GIVEN AN ORAL DOSE OF 0.2μc NaI–131 AT TIME ZERO

E. Body weight changes in hypoxia-exposed and food-deprived rats.

Body weight changes were measured to assess the metabolic response of rats to hypoxia exposure since it was observed that in all instances feeding and drinking activity ceased with hypoxia exposure. Figure 8 summarizes these data. In experiment one it was found that hypoxic rats experienced a markedly greater body weight loss than their corresponding controls (Groups A and B). In experiment two it was found that food deprivation followed by hypoxia-exposure resulted in greater weight loss than food deprivation alone (Groups C and D).

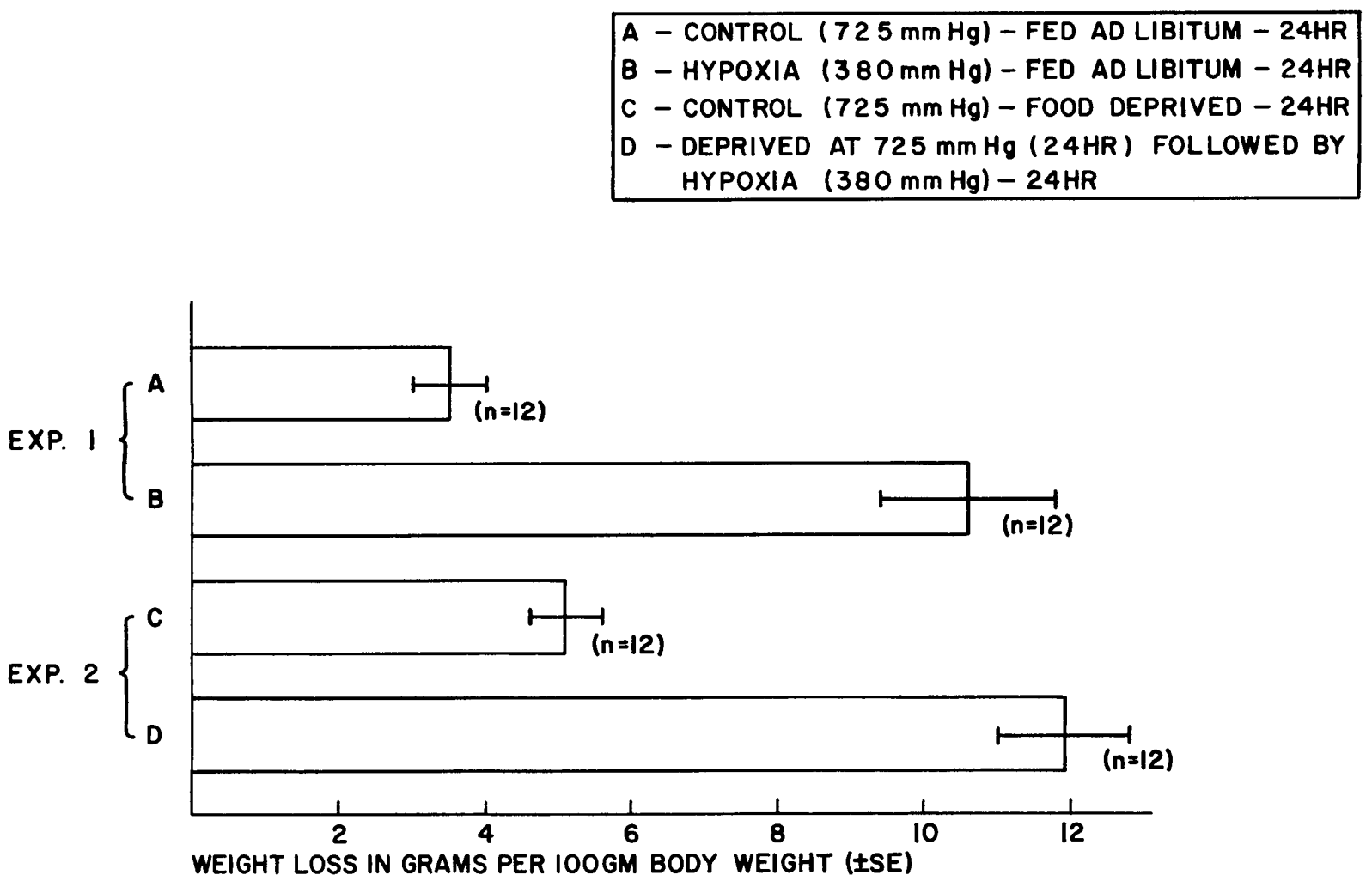

FIG. 8 EFFECT OF HYPOXIA AND FOOD DEPRIVATION ON BODY WEIGHT OF HOLTZMAN RATS

DISCUSSION

One major finding of the present study was that radioiodide absorption in the gastrointestinal tract was markedly reduced with 24 hours altitude exposure. It was shown that this was an indirect result of two hypoxia induced alterations in digestive function: (a) an inhibition of gastric motility and (b) a reduction in food and iodide absorption. The reduced gastric emptying rate is in keeping with an early observation by Crisler *et al.* (6) that low oxygen tension stimulates the vagus nerve and results in pyloric sphincter closure. Thus, hypoxic rats retained more food and iodide in the stomach than controls. In addition to inhibiting the transport of food from the stomach to intestines, hypoxia exposure also inhibited food and iodide absorption. This was evidenced by the finding that gastric food remained undigested and there was a net reduction in intestinal absorption of iodide. In short, the uptake of dietary iodide was markedly reduced in the first day of hypoxia exposure.

A second finding was that circulating titres of radioiodide were maintained at control levels despite a reduced intestinal iodide absorption. It was further shown that blood iodide titres remain within the control range in part due to a diminished removal of circulating iodide *via* metabolic and excretory routes. Support for this stems from data showing that hypoxic rats exhibit decreased renal excretion of radioiodide coupled with lowered thyroidal uptake of iodide.

The latter observation that hypoxic rats exhibit low 24 hour thyroidal iodide uptake was somewhat surprising since iodide trapping is known to be a function of circulating titres of iodide. There are two possible physiological responses during hypoxia exposure which could account for the observed result. One is a decrease in iodide circulation time (influenced by hemal and nutritive changes) which would effect a net reduction in the rate of thyroidal iodide uptake per unit time from the iodide pool; the other is an inhibition of pituitary TSH output and of consequent reduction in the size of the thyroid gland. Data from the present work and other studies indicate that both mechanisms are probably operative within the first 24 hours of exposure.

That hypoxia induces lethargy and an almost complete cessation of locomotor activity has been observed by many workers. Since venous muscle massage is important in facilitating blood flow, it is reasonable to assume that there is a reduction in blood circulation during the early stages of hypoxia. In this regard, several workers have reported a marked shift in distribution of blood from peripheral to internal circulation with hypoxia exposure (4, 24). This visceral pooling of blood, coupled with the decreased muscle tone and decreased gastrointestinal motility, may reduce the transport of iodide from visceral areas to the thyroid. An added factor which contributes to the observed reduction in thyroidal iodide uptake is a decrease in the amount of thyroid tissue capable of taking up iodide. It is difficult to explain how a rapid loss in

tissue mass can occur within a few hours. However, the data of the present study clearly show a decrease in thyroid weight in hypoxic rats whether one calculates this on an absolute or relative weight basis (Table 8, Appendix).

On the basis of the above findings it appears that reduced thyroidal activity is an important feature of the first few hours of hypoxia acclimation. Apparently several systemic responses are involved in the initiation of hypoxia acclimation. One is an immediate cessation of locomotor, feeding, drinking and associated behavioral activities observed by all workers in this field. The consequences of hypoxia-induced lethargy, aphagia and anorexia are a rapid decrease in dietary iodide intake coupled with a decreased iodide excretion rate. Hemal changes, notably the pooling of blood in visceral regions, would also decrease transport of iodide from visceral regions to the thyroid gland. In other words, there is a general lowering of many bodily functions during the first day of exposure.

Since food consumption and absorption are decreased during the initial stage of hypoxia exposure, there is a marked reduction in the oxygen requirements for metabolism of food stuffs as well as for muscular activity. Thus, the reduction in iodide metabolism and thyroid activity simply constitutes one aspect of a generalized reduction in metabolism and utilization of oxygen.

Although it appears that limited dietary iodide intake is of prime importance in initiating lowered thyroid function, a supple-

mental mechanism exists to insure a continued reduction in thyroidal activity, that is, the inhibition of pituitary TSH by relatively high circulating iodide. At any rate, there is no question that rats are in a hypothyroid state during the onset of hypoxia exposure and as others have shown remain hypothyroid after prolonged exposure.

Most workers have agreed that hypothyroidism is an essential feature of the fully acclimated animal and there is ample evidence to demonstrate that chronic exposure results in reduced thyroid function (14, 15, 21, 27). On the other hand, there has been considerable controversy regarding the exact role of the thyroid during the very onset of acclimation. Some have claimed increased (8, 15, 21), other decreased (32, 33, 35) and still others no change (32, 35) in thyroid function during the critical period of the animal's initial adjustment to oxygen lack. An important contribution of this study is that it shows how most of the paradoxical findings can be resolved if one interprets thyroidal responses in light of hypoxia induced changes of food consumption and iodide metabolism.

A number of workers have reported increased thyroidal uptake of injected I-131 in hypoxic exposed rats fed on an ad libitum regimen but which exhibited minimal food intake. Harclerode (15) concluded that increased I-131 uptake reflects a decreased hormone release. DeBias (8) interpreted similar data as signifying a hyperfunctional thyroid whereas Nelson (20) suggested this may reflect a decreased dietary iodide availability. Neither Harclerode nor DeBias con-

sidered the possibility that their animals were iodide deficient. Also, DeBias pre-treated his rats with a pharmacological dose (40 μg/day) of thyroxine and thereby induced a hyperthyroid condition. Nelson's study was primarily directed at clarifying the effect of hypoxia on biosynthesis and peripheral metabolism of thyroxine using radiochromatographic analysis of thyroid gland hydrolysates. Thus, the basis for Nelson's suggestion that increased I-131 uptake might be the result of hypoxia-induced iodide deficiency was a chance finding in one of his experiments that pre-treatment of rats with a maintenance dose (10 μg) KI resulted in a lowered thyroidal I-131 uptake of an injected dose of NaI-131. Nelson correctly surmised that increased thyroidal uptake which both he and others observed in 24 hour exposed rats could simply be due to an iodide insufficiency brought about by low food intake. However, he made no attempt to verify this experimentally.

In brief, a re-analysis of earlier work in which increased iodide uptake occurred on day one of exposure reveals that in all cases hypoxic rats consumed no food and received no supplemental dietary iodide. Since these rats would be presumed to be iodide deficient relative to corresponding controls, any conclusions relative to hypoxia-induced alterations in thyroid function would not be warranted.

A more reliable procedure for assessing thyroidal changes during hypoxia would be to pretreat both experimental and control rats with a small dose of iodide as Nelson did or to have both

groups on an iodide deficient diet prior to hypoxia exposure. Significantly, in two instances where thyroidal response was studied in iodine deficient rats (32, 37), both demonstrated a lowered thyroidal I-131 uptake in hypoxic rats relative to controls.

It is reasonable to assume that a moderate altitude, e.g. 8,000-10,000 feet above sea level, normal thyroid function would be maintained as was shown in two instances (32, 35). This would be expected since there is not as marked a reduction in feeding, drinking, and locomotor activity as one sees in severe hypoxia-exposed animals. As a consequence, reduction in dietary iodide intake would not be as severe.

The present study substantiates the concept that reduced thyroid function is an important feature of the early stages of hypoxia acclimation. The findings further indicate that reduced thyroid function is a consequence of reduced availability of dietary iodide during the first day of exposure, rather than a result of hypoxia per se. The main mechanism involved is a decreased movement of iodide from the stomach to intestines rather than simply a decreased food intake.

SUMMARY

The aim of the present study was to establish the effect of hypoxia on gastrointestinal absorption of orally administered radioiodide and to determine the extent to which this influences circulating and thyroidal iodide levels. A total of 48 adult male Holtzman rats was used in two experiments. In experiment one, 12 rats were placed in a decompression chamber for 24 hours with 12 controls kept at ambient pressures. Both groups were fed ad libitum. In experiment two, 24 rats were food-deprived for 24 hours and subsequently 12 of these were subjected to hypoxia for 24 hours and 12 kept at ambient pressure as food-deprived controls for 24 hours. In all instances, 0.2 μc NaI-131 was given orally 24 hours prior to killing the rats.

The major results were as follows: First, in both experiments hypoxic rats had more food and radioiodide remaining in the stomach than ambient pressure controls. This indicated hypoxia causes a delay in the movement of gastric food and iodide into the intestine where it is normally absorbed. Food deprivation alone had no effect on gastric or intestinal levels of radioiodide indicating no appreciable impairment in iodide absorption.

Second, it was observed that circulating levels of radioiodide were comparable in control and hypoxic rats despite a lowered intestinal absorption in hypoxic animals. This was attributed in part to an hypoxia-induced reduction in urinary excretion of radioiodide.

Finally, one day of hypoxia exposure caused a reduced 24-hour

thyroidal I-131 uptake. This was attributed to a decrease in thyroid gland size. Plasma I-131 levels were not found to be reduced in hypoxic rats.

On the basis of the combined data it is proposed that the initiation of reduced thyroid function during acute hypoxia is probably indirectly mediated through the inhibition of nutritive and renal functions. One important response is a decreased intestinal absorption of iodide which is needed for thyroid hormone formation by a hypoxia-induced delay in gastric emptying. Another response is a maintenance of iodide levels within the control range due in part to a decreased renal iodide excretion.

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APPENDIX

Summary Tables of the Data

Table 1. Gastrointestinal absorption of orally administered NaI-131 in hypoxia-exposed and food-deprived rats.

Percent NaI-131 remaining in gastrointestinal tract ($\bar{x}$±S.E.)					
Experiment	Group	Stomach	P*	Small Intestine	P*
1	A(12)**	1.2±0.2	0.001	0.4±0.1	NS
	B(12)**	30.8±4.8		0.5±0.1	
2	C(12)**	1.4±0.2	0.01	0.5±0.1	NS
	D(12)**	23.6±6.8		1.4±0.4	

*Probability values were calculated using the t test.
**Numbers in parenthesis indicate number of rats used.

Table 2. Gastrointestinal digestion and absorption in hypoxia-exposed and food-deprived rats.

Grams of food remaining ($\bar{x}$±S.E.)					
Experiment	Group	Stomach	P*	Small Intestine	P*
1	A(12)**	0.3±0.0	0.001	1.3±0.2	0.01
	B(12)**	3.5±0.4		2.5±0.3	
2	C(12)**	0.3±0.0	0.01	1.7±0.2	NS
	D(12)**	2.6±0.6		1.5±0.1	

*Probability values were calculated using the t test.
**Numbers in parenthesis indicate number of rats used.

Table 3. Plasma radioiodide levels of hypoxia-exposed and food-deprived rats.

Percent I-131 in plasma ($\bar{x}$±S.E.)			
Experiment	Group	Plasma I-131	P*
1	A(12)**	1.9±0.3	NS
	B(12)**	2.8±0.7	
2	C(12)**	2.0±0.4	NS
	D(12)**	3.4±0.7	

*Probability values were calculated using the t test.
**Numbers in parenthesis indicate number of rats used.

Table 4. Thyroidal radioiodide content of hypoxia-exposed and food-deprived rats.

Percent I-131 in the thyroid ($\bar{x}$±S.E.)			
Experiment	Group	Thyroid I-131	P*
1	A(12)**	11.2±1.8	0.05
	B(12)**	6.6±0.9	
2	C(12)**	8.7±0.5	0.01
	D(12)**	5.2±0.8	

*Probability values were calculated using the t test.
**Numbers in parenthesis indicate number of rats used.

Table 5. Urinary radioiodide levels of hypoxia-exposed and food-deprived rats.

Percent I-131 in urine ($\bar{x}$±S.E.)			
Experiment	Group	Urinary I-131	P*
1	A(12)**	40.7±3.4	0.01
	B(12)**	23.0±2.9	
2	C(12)**	42.2±4.3	0.001
	D(12)**	16.7±3.3	

*Probability values were calculated using the t test.
**Numbers in parenthesis indicate number of rats used.

Table 6. Urinary excretion volumes of hypoxia-exposed and food-deprived rats.

ml/rat ($\bar{x}$±S.E.)			
Experiment	Group	Urinary volume	P*
1	A(12)**	15.9±2.4	NS
	B(12)**	11.4±1.1	
2	C(12)**	10.0±1.6	NS
	D(12)**	13.4±1.9	

*Probability values were calculated using the t test.
**Numbers in parenthesis indicate number of rats used.

Table 7. Fecal radioiodide levels of hypoxia-exposed and food-deprived rats.

Percent I-131 in feces ($\bar{x}$±S.E.)			
Experiment	Group	Fecal I-131	P*
1	A(12)**	2.1±0.6	NS
	B(12)**	2.0±0.3	
2	C(12)**	2.2±0.3	NS
	D(12)**	0.5±0.1	

*Probability values were calculated using the t test.
**Numbers in parenthesis indicate number of rats used.

Table 8. Body weight loss of hypoxia-exposed and food-deprived rats.

Grams lost/100 g body weight ($\bar{x}$±S.E.)			
Experiment	Group	Grams	P*
1	A(12)**	3.5±0.5	0.001
	B(12)**	10.6±1.2	
2	C(12)**	5.1±0.5	0.001
	D(12)**	11.9±1.4	

*Probability values were calculated using the t test.
**Numbers in parenthesis indicate number of rats used.

Table 9. Thyroid weight changes in hypoxia-exposed and food-deprived rats.

Experiment	Group	mg Thyroid	P*	mg Thyroid/ 100mg Body Weight	P*
1	A(12)**	15.3±0.3	0.001	5.4±0.2	0.01
	B(12)**	10.8±0.3		4.3±0.2	
2	C(12)**	14.4±0.2	0.001	6.1±0.3	0.001
	D(12)**	9.9±0.4		4.0±0.1	

*Probability values were calculated using the t test.
**Numbers in parenthesis indicate number of rats used.